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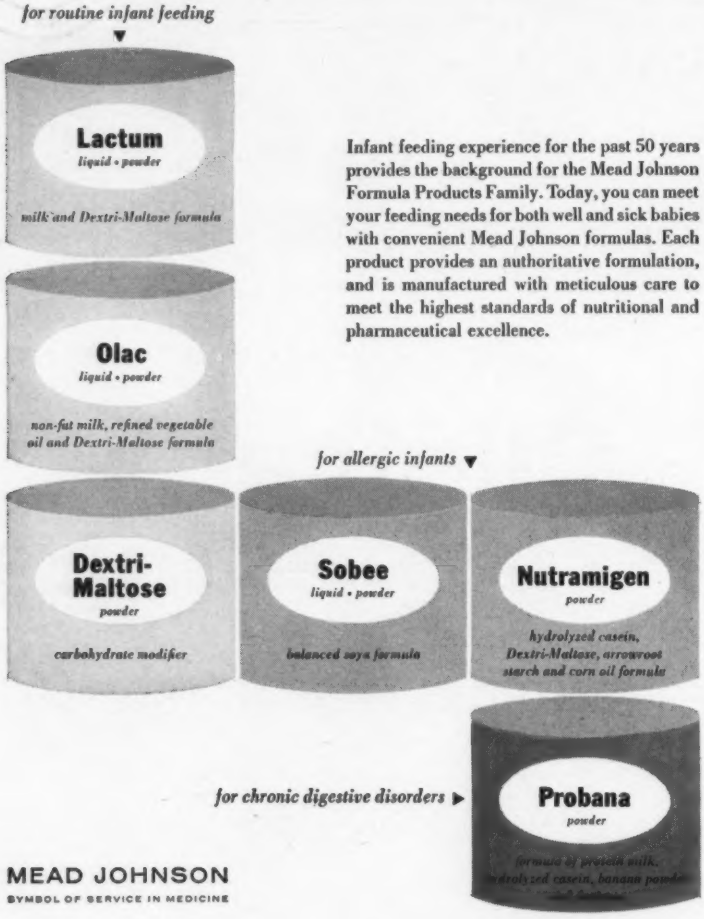

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SALMONELLA INFECTIONS

Norman B. McCullough, M.D., Ph.D.*

INTRODUCTION

The genus Salmonella comprises nearly 300 species or serotypes of closely related organisms. A system of antigenic analysis, the Kauffmann-White schema[1] is employed for identification. This system divides the genus into groups on the basis of somatic antigens, and into species according to flagellar antigenic components. Thus each species has a distinctive formula denoting the presence of certain somatic and flagellar antigens For emphasis of the disease potentialities of the entire genus, it is well to remember that group A contains *Salmonella paratyphi* (paratyphi A); group B, *Salmonella schottmuelleri* (paratyphi B); group C, *Salmonella hirschfeldii* (paratyphi C); and group D, the causative organism of typhoid fever, *Salmonella typhosa*.

CASE REPORT

The patient, a Negro boy aged 3 years, 9 months, was admitted to Children's Hospital on February 24, 1957 with abdominal pain, fever, and a stiff neck. One week prior to admission there was onset of abdominal pain without nausea or vomiting. He had been seen at another hospital where a diagnosis of tonsillitis was made, and he was given two injections and some liquid medicine to take at home. The abdominal pain had persisted; he became feverish and complained of his neck hurting, particularly on turning and flexing. Anorexia developed two days prior to admission and he refused everything by mouth except a small amount of fluids. There were two loose stools two days prior to admission, and one on the day of admission.

The past history was non-contributory; he had previously had measles, mumps, and chicken pox but no other serious illnesses or operations. He had been hospitalized at 1 year of age after ingesting cleaning fluid but had recovered without sequelae. He had been immunized against diphtheria, pertussis, and tetanus during the first year of life but had not been vaccinated against smallpox or immunized against poliomyelitis or Salmonella. The developmental history was normal.

The mother, father, and two sisters were living and well. There was no history of exposure to contagious disease or ingestion of contaminated water or milk. The mother worked as a food handler.

Examination on admission revealed a fretful child who complained of a sore and stiff neck. The rectal temperature was 105 degrees. His head was tilted markedly to the left. His eyes and ears were normal; his throat and tonsils were inflamed; there were enlarged left submandibular lymph nodes. There was considerable resistance of the neck to flexion, but no meningeal signs. The lungs and heart were normal. The pulse rate was 140 per minute. The abdomen was not tender to palpation and no organs or masses were felt. Rectal examination was negative. The extremities were

* Chief, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda 14, Maryland.

normal. His skin was hot and dry. Diagnostic impressions on admission to the hospital were acute pharyngo-tonsillitis and adenitis, myositis of the left side of the neck, and possible urinary tract infection.

The blood count on admission revealed a hemoglobin of 8.3 gm. per 100 ml., a white blood cell count of 10,000, with 63 per cent segmented forms, 8 per cent band forms, and 29 per cent lymphocytes; platelets were adequate. His urine showed a specific gravity of 1.021, 30 mg. of albumin per 100 ml., and 2 plus acetone.

Blood and urine cultures were taken on admission. A skin test using intermediate strength PPD (Tuberculin), and a sickle cell preparation were done; the results of both were negative. He was placed at bed rest and given supportive therapy. The day following admission treatment with aqueous penicillin was commenced; he received 600,000 units every 4 hours. A repeat blood culture and a spinal puncture were done on the second hospital day. The spinal fluid contained one lymphocyte per cu. mm. and a normal content of sugar and protein. Agglutination tests gave the following results: Typhoid H 1:80, Salmonella group D 1:160, and Salmonella group E 1:40. One week later the group D Salmonella titre had risen to 1:320. *S. typhosa* was isolated from the two blood cultures. Stool cultures were consistently negative.

With the diagnosis established, penicillin was discontinued and specific therapy instituted. Chloramphenicol was given intravenously, 500 mg. every 6 hours for one week, and continued intramuscularly for an additional week at half that dosage.

His temperature remained septic during the first 5 days of hospitalization and ranged from 101 to 105 degrees daily, but slowly dropped to normal by the sixth hospital day. His course thereafter was uneventful and he was discharged clinically well, to be followed in the Out Patient Clinic.

COMMENT

In the case presented today the onset was somewhat atypical. The presence of inflammation of the throat and tonsils led to the diagnosis of tonsillitis and pharyngitis. A moderately but not a severely inflamed throat is common in typhoid, and the typhoid organism has been recovered in culture from tonsils. Cervical myositis with interference to flexion of the neck also afforded confusion. Myositis occurs in typhoid fever, but involvement of the neck muscles is unusual. The patient had neither a leucopenia nor a slow pulse. The disparity between pulse rate and degree of fever is present less consistently in children than in adults and is usually absent in the mild case. The continued fever and abdominal distress were suggestive of systemic disease. Positive blood cultures and a rising antibody titre established the diagnosis. Stool cultures were negative, but this is not unusual early in the disease. Retrospectively, the entire symptomatology is explainable on the basis of the primary diagnosis of typhoid fever. There was prompt clinical response to treatment with chloramphenicol.

DISCUSSION

Although the incidence of typhoid fever in the United States has reached a very low level, the total disease incidence due to Salmonella species is very great, perhaps rivaling the "common cold" in frequency.

The Salmonella are responsible for 3 main types of illness: a) enteric fever, the classical example being typhoid fever, b) gastroenteritis or "food infection", and c) Salmonella septicemia or Salmonella fever. There are, of course, gradations within and between these main types, or one type of illness may merge into another.

ENTERIC FEVER

Typhoid Fever

Typhoid fever is characteristically a disease of slow effervescence. The patient usually cannot state exactly when he became ill. There are complaints of malaise, anorexia and headache, followed by fever which increases in a step-wise manner to 103–105 degrees, and then remains continually high until death or convalescence ensues. The pulse tends to be slow in comparison to the height of the fever. Nosebleeds are common; there may be diarrhea, although constipation is more often the rule, accompanied by abdominal tenderness and distension. A dry cough is frequently present. Toward the end of the first or during the second week rose spots appear and splenomegaly is commonly present. In the more severe cases, with continued elevation of temperature, the patient appears prostrate, stuporous, may become delirious, and presents the so-called "typhoid state". In non-fatal cases after the third week the temperature curve shows morning remissions, and there is a gradual return to normal by slow lysis.

Typhoid fever is a disease prone to complications and relapse. Following ingestion of food or water containing typhoid bacilli, the organisms localize in Peyer's patches and other lymphoid tissue in the lower ileum. After an incubation period of 7 to 14 days the bacteria gain entrance to the blood stream and the patient becomes ill. The organisms are widely disseminated throughout the body and tend to localize in various tissues. Commonly there is focal necrosis in the liver, and the gallbladder is always infected. Acute cholecystitis may develop. Empyema, periostitis, localization in joints, lungs, or other soft tissues may occur. Osteomyelitis may develop even months after convalescence. This lesion is essentially benign and tends to heal. Relapses occur in 10 per cent of cases, significant hemorrhage from the bowel in 5 per cent, and intestinal perforation in 1 per cent. Twenty per cent of patients continue to shed the organism in the stool for weeks; from 1 to 3 per cent become permanent carriers. The death rate in typhoid fever is variable, ranging from 10 to 20 per cent in untreated cases.

A leucopenia and relative lymphocytosis are present in most cases. Blood cultures are usually positive during the first and second weeks of the disease; stool cultures may be positive from the beginning but more usually are negative and become positive later in the course. In the second week

and thereafter, agglutinins are present in the blood, and their detection is useful in diagnosis. Since rise in antibodies to H, O, and Vi antigens may occur independently, to detect all cases of the disease, it is necessary to employ all three antigens, although it is rare for Vi agglutinins to appear in the complete absence of H or O agglutinins. A rise in titre of specific agglutinins, or an O titre of 1:50 or higher in a non-vaccinated patient is presumptive evidence in support of the diagnosis of typhoid fever. In the previously immunized patient, the O titre is of most value, since an H titre may persist for years while an O titre falls or disappears within six months to a year after immunization.

Chloramphenicol is an effective drug. The adult dosage is 3 or 4 grams per day until fever is gone, then 2 grams per day. The treatment should be continued until the patient has been afebrile for 7 to 10 days. Dosage for children is scaled down on a weight basis for those weighing over 60 pounds. Infants and younger children should receive 75 to 150 mg. per kg. to start, decreasing to 50 mg. per kg. While chloramphenicol therapy has lowered the death rate to five per cent or less, the incidence of hemorrhages, perforations, and permanent carrier states has been affected little if at all.

Paratyphoid Fever

Enteric fever (paratyphoid fever) due to Salmonella species other than *S. typhosa* usually has a shorter incubation period (1 to 10 days) than typhoid and presents a milder and less typical course, although *S. paratyphi*, *S. schottmuelleri* and *S. hirschfeldii* may produce as severe illness as the typhoid organism itself. In the United States, next to *S. typhosa*, *S. schottmuelleri* is the most common cause of enteric fever; numerous species may produce this illness.

GASTROENTERITIS

The most common manifestation of infection by the *Salmonella* organisms is gastroenteritis or "food infection". With the exception of *S. typhosa*, probably all the members of the genus may cause this illness. Classically, the disease is characterized by a relatively short incubation period, abrupt onset, abdominal cramps or discomfort, nausea, vomiting, diarrhea and fever. A few years ago we studied experimental salmonellosis in human volunteers by feeding organisms of 6 species and 12 strains in graded dosages to several hundred persons. Dosages producing disease ranged from 125,000 to 5,000,000,000 organisms. In general with any particular strain a certain dosage was necessary to produce illness. When smaller numbers were fed they were demonstrable in the stool for variable periods lasting from several days to several months. In these instances the subjects were asymptomatic and developed no agglutinins with the single exception

that those receiving *Salmonella pullorum* usually exhibited an antibody rise. *Salmonella*, then, may be ingested and not give rise to illness, but may cause transient carrier states. This is probably a common occurrence. Whether illness results seems dependent on the number of organisms ingested.

In these studies there resulted 100 cases of clinical illness. The range of symptomatology was great. Nausea, vomiting, prostration, abdominal cramps, fever, and diarrhea, singly or in any combination, were observed. Illness lasted from a few hours to 2 or 3 weeks, with all gradations of severity. Incubation periods ranged from 4 hours to 7 days with the majority falling between 18 and 42 hours. Fever was present in all who had significant illness. This is a differential point between Salmonella gastroenteritis and staphylococcic food poisoning in which fever is absent. Also, in staphylococcic food poisoning the incubation period does not exceed 3 hours. Of the subjects in this series who became ill, approximately one third exhibited a rise in specific agglutinins, and then usually after convalescence. The agglutination test is of little value in the diagnosis of Salmonella gastroenteritis. Stools are regularly positive from the onset. Indicated treatment is non-specific and supportive.

SALMONELLA SEPTICEMIA (SALMONELLA FEVER)

Complicating a gastroenteritis, or initially in the complete absence of abdominal complaints, Salmonella may invade the blood stream and cause a septicemia. In the absence of localizing complications the illness may be of short duration. The organisms may, however, localize in any tissue of the body. The more common complications of this nature are abscesses in the perineal and pelvic regions, cholecystitis, endocarditis, pericarditis, pyelonephritis, meningitis, suppurative arthritis, pneumonia, empyema, and osteomyelitis. Blood cultures in these cases may be negative or only positive intermittently. Fever may be prolonged. In any fever of undetermined origin, salmonellosis should be suspected and appropriate cultural and serological tests done. A search should be made for a localized lesion including a radiographic survey of the skeleton to detect an osteomyelitis. We currently have such a case under study with osteomyelitis and collapse of two vertebrae due to infection with *Salmonella oranienburg*. Serologic titers are usually diagnostic. The organism is often present in the stool from the start of the illness, though stools may be negative at the time study of a localized lesion is undertaken.

TREATMENT

Other than for typhoid fever there is no standard therapy for the Salmonella infections. Paratyphoid fevers apparently respond clinically to chloramphenicol, but studies definitely establishing the value of this

drug are lacking. Localized disease often requires surgical treatment in addition to the use of antibiotics. Chloramphenicol probably has value in the therapy of all Salmonella infections, but to a lesser extent than in typhoid fever. We have treated cases successfully with combinations of chloramphenicol and tetracycline, and others with dihydrostreptomycin added to this combination.

THE CARRIER STATE

The organism most prone to cause the chronic carrier state is *S. typhosa*, although numerous species may do so. The bacteria are found in the gall bladder, or less frequently in kidney tissue, and appear in the stool or urine. Many cases give no antecedent history of clinical illness. Treatment of the carrier state is unsatisfactory. A small proportion of cases are cured by cholecystectomy. Antibiotic therapy has so far been disappointing, although some cures have resulted.

IMMUNIZATION

A vaccine containing dead organisms of *S. typhosa*, *S. paratyphi*, and *S. schottmuelleri* has been used extensively for prophylaxis. While definitive data are difficult to obtain there is little question that such immunization is of considerable value. However, immunized persons may contract the disease when heavily exposed. The drop in incidence of typhoid fever in parts of the western world in recent decades is primarily due to advances in general sanitation, water purification and sewage disposal.

While an attack of typhoid fever, and presumably of enteric fever due to any other species of Salmonella provides a high degree of immunity, an attack of Salmonella gastroenteritis is followed by measurable but not marked immunity.

In experimental studies, human volunteers were refed the same species which had previously produced illness. Approximately two thirds of these subjects again became ill upon receiving the same or slightly increased dosage of organisms. Whether parenteral immunization will protect against gastroenteritis has not been experimentally determined.

EPIDEMIOLOGY

All of the Salmonella are parasitic for man or animals, and do not persist indefinitely in the free-living state. Epidemiologically there are two groups: those found only or predominantly in man, and those occurring primarily in other animals but which may produce disease in man. In the former group are *S. typhosa*, *S. paratyphi*, *S. schottmuelleri*, and *S. hirschfeldii*. Man acquires these infections from ingestion of food or drink contaminated with fecal matter deriving from active cases or carriers. Preven-

tion of these infections, of course, is dependent upon purification of water supplies, adequate sewage disposal practices, and the exclusion of human carriers from the preparation and handling of food. The latter group of Salmonella comprises all the rest of the species. The two greatest reservoirs are rodents and fowls. Of these, rats, mice, and domestic poultry constitute the main hazards for man. To be sure, once human cases or carrier states occur, the epidemiology common to the first group obtains, but primarily most infections arise from direct contamination of food by infected rats and mice, or the consumption of contaminated poultry products.

Prevention of rat and mouse-borne disease is relatively simple, requiring the safeguarding of food from contamination by these rodents. Poultry-borne disease is another matter. Over 50 species of Salmonella occur in chickens. Some few of these, and in particular *S. pullorum*, may infect the ovary of the laying hen and thus be present inside the newly laid egg. Even the best grade A eggs may then contain Salmonella. The others occur in the intestinal tract and contaminate the shell of the egg during laying. Egg shell is porous and any organisms found on the outside may penetrate the shell, especially under poor storage conditions; even so, the number of organisms within a market egg are usually insufficient to produce illness. Broken egg products present a more serious problem. During breaking, organisms on the shell are bathed in and contaminate the product. Thus, spray-dried egg powder, egg whites, and frozen egg yolks probably always contain numerous Salmonella organisms; the only question in regard to a particular lot is: how many organisms? Spray-dried egg has been a notorious source of Salmonella infection for man. Currently, frozen egg yolk is used extensively in the food industry. None of these products should be used in foods not sufficiently heated thereafter to kill all the organisms. A temperature of 350 degrees for 30 minutes is the minimum required.

Recently we had a small epidemic (40 cases) of salmonellosis at the Clinical Center, National Institutes of Health, which was traced to the use of frozen egg yolk. The offending organism, *Salmonella tennessee*, was recovered from the cases and repeatedly from the frozen egg product. In spite of adequate knowledge of the subject, this product had been inadvertently used in buttercream frosting for cakes, and in special pie served only occasionally; neither was heated sufficiently to kill the organisms.

Meat derived from infected animals may be a source of infection. Infected turkeys have caused numerous outbreaks. Roast turkey, prepared at home, may be consumed over a period of several days; in commercial establishments it is commonly held on a steam table and served over a

period of several hours; at social gatherings it may be kept at room temperature and offered to guests over an extended period. In all of these situations Salmonella organisms not killed by heat of roasting are allowed an opportunity to multiply.

Except for originally heavily contaminated foods, the risk of salmonellosis is dependent upon multiplication of organisms prior to consumption of the food. Foods which may contain Salmonella should be consumed promptly after preparation, or be adequately refrigerated, to minimize the opportunity for bacterial growth. Broken egg products, in particular, should be used only in baked goods, or in foods heated sufficiently to kill all the organisms.

BIBLIOGRAPHY

KAUFFMANN, F.: The Diagnosis of Salmonella Types. Charles C. Thomas, Publisher, Springfield, Illinois, 1950.

McCULLOUGH, N. B., AND EISELE, C. W.: Experimental Human Salmonellosis. I. Pathogenicity of Strains of *Salmonella meleagridis* and *Salmonella anatum* Obtained from Spray-Dried Whole Egg. J. Infect. Dis., **88:** 278, 1951.

McCULLOUGH, N. B., AND EISELE, C. W.: Experimental Human Salmonellosis. III. Pathogenicity of Strains of *Salmonella newport*, *Salmonella derby*, and *Salmonella bareilly* Obtained from Spray-Dried Whole Egg. J. Infect. Dis., **89:** 209, 1951.

McCULLOUGH, N. B., AND EISELE, C. W.: Experimental Human Salmonellosis. IV. Pathogenicity of Strains of *Salmonella pullorum* Obtained from Spray-Dried Whole Egg. J. Infect. Dis., **89:** 259, 1951.

McCULLOUGH, N. B., AND EISELE, C. W.: Experimental Human Salmonellosis. II. Immunity Studies Following Experimental Illness with *Salmonella meleagridis* and *Salmonella anatum*. J. Immunol., **66:** 595, 1951.

MORGAN, H. R.: The Salmonella. In: Bacterial and Mycotic Infections of Man (Edited by René J. Dubos), 2nd Ed., J. B. Lippincott, Philadelphia, 1952.

CHRONIC ADRENAL INSUFFICIENCY IN CHILDHOOD

Jose R. Puig, M.D.,* Joseph M. LoPresti, M.D.†

INTRODUCTION

The following case history is reported because it typifies the rather rare disorder of chronic adrenal insufficiency (Addison's Disease) as it occurs in childhood. In addition, it affords the opportunity to point out some of the necessary diagnostic criteria for establishing the diagnosis

* Research Fellow, Research Foundation, Children's Hospital.

† Associate Staff, Director, Medical Education, Children's Hospital; Associate Professor, Pediatrics, George Washington University School of Medicine.

TABLE I

Blood Chemistries

Date	CO_2	Na+	K+	Cl−	Ca++	Blood Sugar	BUN
	Vol. %	*mEq./L.*	*mEq./L.*	*mEq./L.*	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*
March 10	24			92			
11	21	110	6	90	9.7	102	15
12	31	112	3.3	92			
13	31	120	2.7	98			
14	43	122	3.8	96			
15	39	124	3.7	104			
16	49	136	4.5	104			
17	58	138	4.5	104			
18	52	136	4.3	108			
April 5	52	145	3.9	116			

and some of the pitfalls which may be encountered during therapy for this disease.

CASE REPORT

A 10 year old white male child was admitted to Children's Hospital* on March 10, 1957 because of vomiting and dehydration without anorexia. Ten days before admission listlessness and irritability developed. The patient complained of "feeling tired" and could not perform his daily routines. These symptoms continued for one week at which time vomiting appeared. Within 24 hours, emeses of gastric contents occurred after every attempt to feed. Within a short period retching became constant. One day before admission the patient complained of generalized abdominal pain. During this time no fever, diarrhea, visual disturbance, or headache were noted, and he was urinating freely. In the 24 hour period preceding hospitalization, generalized muscular twitchings which occurred during sleep were seen by his mother. He was admitted to a neighboring hospital where intravenous fluid therapy with Ringer's lactate solution was started. The initial laboratory studies were reported as showing an erythrocyte count of 5.2 million per $mm.^3$, a hemoglobin concentration of 15 gm. per 100 ml., a leucocyte count of 10,900 per $mm.^3$, a blood sugar level of 55 mg. per 100 ml., a serum chloride level of 61 mEq. per liter, and a carbon dioxide combining power of 18 mEq. per liter. The child continued to vomit and was transferred to this hospital.

The only significant feature of the past history was a marked craving for salt, vinegar, and buttermilk which had been present for the preceding year.

The initial physical examination showed an acutely ill, slender white boy with sunken eyes, poor skin turgor, and severe dehydration. The pulse and respiratory rates were 100 and 18 per minute respectively. The blood pressure was 90/60. The patient weighed 55 pounds (25 kilograms). The abdomen was scaphoid; the deep tendon reflexes were hypoactive; the hands and feet were cold; the remainder of the examination was normal. The important laboratory determinations performed in the hospital are summarized in Table I. Intravenous fluid therapy was started and consisted of a polyionic solution which contained 5 per cent glucose and 150 mEq. of electrolyte per liter. On the next morning (March 11) after blood chemistries were

* Private Service of Winston E. Cochran, M.D.

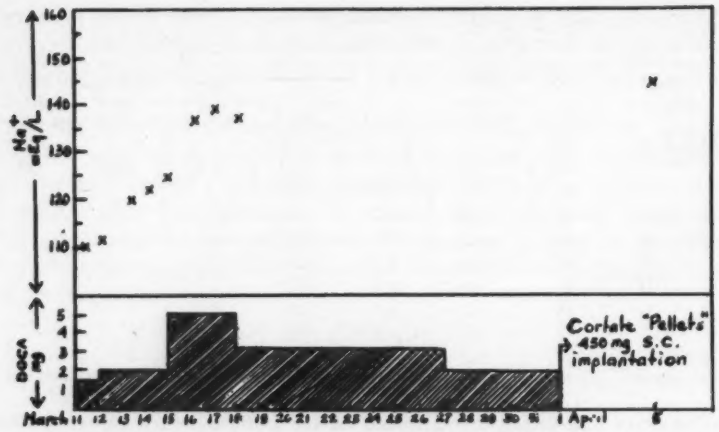

FIG. 1. DOCA administration compared with serum sodium response

reported (cf. Table I), a diagnosis of an acute adrenal crisis was considered and appropriate therapy initiated. The total 24 hour fluid requirement was calculated and administered as 5 per cent glucose in 0.33 per cent sodium chloride, a solution which contains 51 mEq. of chloride per liter. Seventy-five mg. of intravenous glucocorticosteroid (hydrocortisone) was added to the first 500 ml. of this solution. In addition, 1.5 mg. of desoxycorticosterone acetate (DOCA) was injected intramuscularly. The child showed an initial improvement, viz., the vomiting ceased, but he complained of thirst and appeared restless. At 10:30 P.M., he became disoriented and irritable. There were hyperextension and adduction of both lower extremities, incoordinate movements of the right arm, and flexion of the wrists. The pupils were markedly dilated. Respirations were irregular and deep, and the respiratory rate was 28 per minute; the pulse rate was 160 per minute. The intravenous administration of 15 ml. of a 10 per cent solution of calcium gluconate and 210 mg. of sodium phenobarbital failed to control this convulsive-like episode. At this time a diagnosis of water intoxication was considered. All previous intravenous fluids were discontinued. Three hundred ml. of blood plasma was given intravenously, followed by 400 ml. of normal saline with 50 ml. of 50 per cent glucose and 100 ml. of salt-poor albumin. The same fluids were given on the next day (the third hospital day) with the omission of the 50 per cent glucose. Improvement was dramatic and except for brief periods of disorientation and restlessness, the child appeared to be normal. On this day oral fluids were started. On the second, third, and fourth hospital days, desoxycorticosterone acetate (DOCA) was given intramuscularly in a dose of 2 mg. This was increased to 5 mg. on the fifth day when the sodium level was noted to be relatively unaffected by the smaller dose (cf. Figure 1). Thereafter the dose of desoxycorticosterone acetate was gradually diminished to 2 mg. per day until the twenty-second day of hospitalization when 6 pellets (each containing 75 mg. of desoxycorticosterone acetate) were implanted in the infrascapular areas. On the fourth hospital day, intravenous fluids consisted of 500 ml. of normal saline, followed by 500 ml. of 5 per cent glucose in distilled water. On the fifth day intravenous fluid therapy was discontinued because the general condition of the child was markedly improved. A soft diet with a high

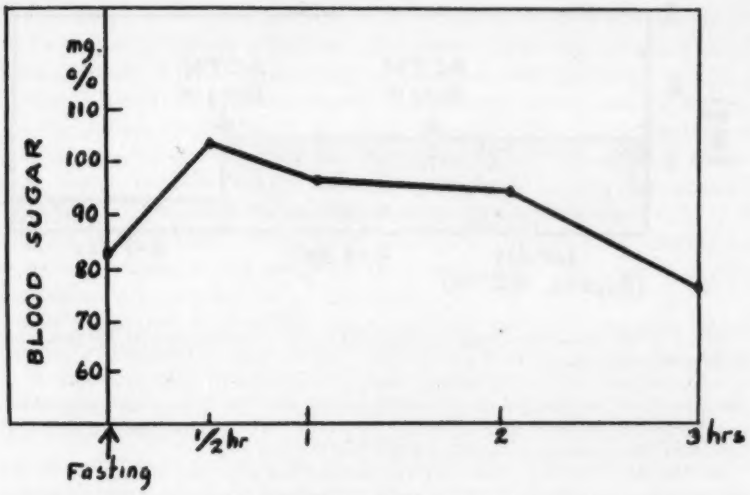

FIG. 2. Glucose tolerance test

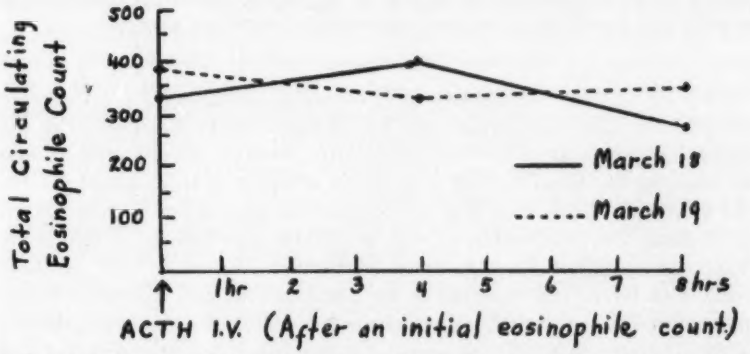

FIG. 3. Total circulating eosinophile count response to ACTH intravenous administration (two successive days).

fluid intake was begun. In addition, 600 mg. of sodium chloride in the form of tablets was given four times a day.

During the patient's hospitalization repeated hemograms and urine analyses were reported as within normal limits. In addition the tuberculin and histoplasmin skin tests were negative, and an x-ray of the abdomen in supine position did not show calcific deposits in the adrenal areas. After the implantation of the DOCA pellets, an oral glucose tolerance test showed a flat curve (Figure 2). On the eighth and ninth hospital days an 8 hour intravenous ACTH test was performed, and the total circulating eosinophils and 17-ketosteroid urinary excretion measured (Figures 3 and 4).

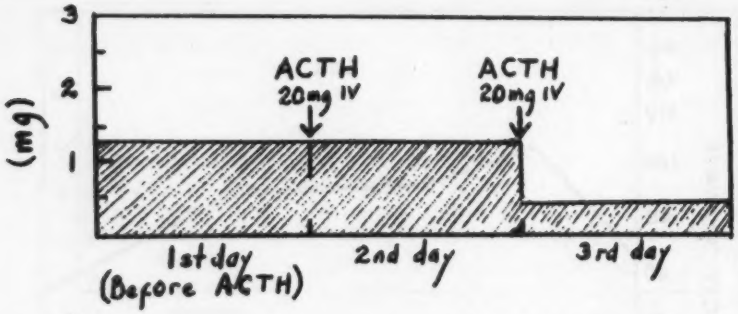

FIG. 4. 17 Ketosteroids urinary excretion (24 hours) in response to ACTH (repeated three consecutive days).

The failure of the circulating eosinophils to fall and the urinary excretion of 17-ketosteroids to increase in response to the intravenous administration of ACTH confirmed the diagnosis of chronic adrenal insufficiency.

On the twenty-fifth hospital day the patient was receiving a regular diet and 600 mg. of sodium chloride as tablets twice a day. His serum sodium level was normal (cf. Table I). The general condition and physical examination were completely normal and he was discharged from the hospital. At the time of this writing, the child has continued to do well and is checked periodically by his private physician.

DISCUSSION

Chronic adrenal insufficiency as it occurs in childhood is a rather rare disorder. It differs somewhat from the disease as it is encountered in the adult. The majority of the cases in children have no definite etiology and at autopsy the usual finding is a simple atrophy of the adrenal glands. An hereditary factor may play a role since the disease has been described in siblings. The relationship of chronic adrenal insufficiency to idiopathic hypoparathyrodism has not been established. However, both of these conditions have been reported in the same patient and idiopathic hypoparathyroidism has been known to occur in a sibling of a child with chronic adrenal insufficiency. The presence of a negative tuberculin skin test and the absence of calcification in the adrenal areas render tuberculosis an unlikely etiologic factor in our patient. It is probable that he has a simple idiopathic atrophy of his adrenal glands.

A number of clinical features serve notice that the adrenals may not be functioning. The initial signs in childhood usually are those of an acute adrenal crisis and this patient was no exception. Vomiting is the cardinal manifestation and the wary physician always considers adrenal insufficiency in the differential diagnosis when this symptom is present. An additional clue is rapid dehydration which does not respond when parenteral fluid therapy is used alone. *The dehydration which accompanies adrenal*

insufficiency can be corrected only by the combination of proper parenteral fluids and supplemental steroid administration. Abdominal pain is usually present in the older child and may be confused with a surgical condition of the abdomen. The authors have been impressed by one clinical finding that is present invariably in an acute adrenal crisis: *in the presence of marked dehydration the patient continues to void freely.* In addition, symptoms which indicate chronic adrenal insufficiency usually are present. The history of salt craving serves as an important clue especially if it appears to be of recent origin, as it was in this patient. Easy fatigability is a manifestation of low serum sodium and chloride. The absence of skin pigmentation is not unusual in childhood.

The laboratory findings are diagnostic and reflect a deficiency of all of the corticosteroids. The serum electrolyte pattern indicates that there is a defective production of the salt regulating adrenocorticosteroids. When present in normal amounts, these cause a retention of body sodium and chloride and a loss of body potassium. In their absence an excessive amount of sodium and chloride are excreted in the urine, and potassium is retained. Since relatively large amounts of electrolyte are lost, the patient becomes hypotonically dehydrated. The serum then will show low sodium and chloride and elevated potassium levels. Extracellular water is lost in two ways in the patient with acute adrenal insufficiency: 1) in the formation of urine to carry the large amounts of electrolyte excreted and 2) in the shift of water into the intracellular space as the extracellular fluid becomes hypotonic. As will be seen later this has an important bearing on therapy. In addition, this intracellular shift of water may result in clinical symptoms. If enough water shifts into the cells of the central nervous system, water intoxication is produced and muscular twitching, disorientation, lethargy, coma and convulsions may be encountered. Other blood changes are related to dehydration, viz., pre-renal azotemia and hemoconcentration usually are present; as this dehydration is usually severe, the patient with acute adrenal insufficiency frequently has symptoms of peripheral vascular collapse. The combination of an elevated blood urea nitrogen together with a low serum sodium and chloride concentration in the presence of a low blood volume points to adrenal rather than renal failure. Deficient production of the adrenal glucocorticosteroids is manifested by low fasting blood sugar level and a flat glucose tolerance curve. There also will be a failure of the total circulating eosinophils to fall in response to the parenteral administration of adrenocorticotropic hormone (ACTH). All of these findings were present in our patient (Figures 2 and 3). The most valuable laboratory aid to the diagnosis is one which measures androgen production by the adrenal cortex. This test is time consuming but may yield highly suggestive results. An initial

24 hour urinary excretion of 17-ketosteroids is measured. During the next 48 hours, 20 mg. of adrenocorticotropic hormone (ACTH) diluted in isotonic saline is administered intravenously over a period of 8 hours each day. Normally, there is a marked increase in urinary 17-ketosteroid excretion. In adrenal cortical insufficiency there is little or no increase (Figure 4). This is one of the most sensitive tests for detecting minor degrees of deficiency.

The patient with an Addisonian crisis is hypotonically dehydrated, i.e., he has lost relatively more electrolyte than water from his extracellular compartment. It is important that the water deficit be repaired but the *immediate need* is for salt in the form of sodium chloride. A failure to recognize this basic principle when treatment is instituted may lead to serious consequences. If a hypotonic sodium chloride solution is used, as it was in this patient, a further dilution of the already hypotonic extracellular fluid will occur. More extracellular fluid will shift into the intracellular space and water intoxication may be produced. It is more rational to administer isotonic or even hypertonic saline initially. One may accurately calculate the amount of normal saline required to correct the sodium deficit in the extracellular fluid from the formula:

(142 minus patient's plasma sodium level in mEq. per liter) multiplied by 25 per cent of patient's weight in kg. This product represents the total sodium deficit in the extracellular fluid. For example, our patient weighed 25 kg. (55 lbs.) and his plasma sodium level when the diagnosis was established was 112 mEq. per liter. The normal extracellular sodium concentration is 142 mEq. per liter. Therefore, the patient's extracellular sodium deficit was 30 mEq. per liter. The total extracellular fluid is 25 per cent of the body weight or, to illustrate in the example: 25 per cent $\times$ 25 kg. equals 6.25 kg. or 6.25 liters of extracellular fluid (since one kg. equals one liter). Then it follows that the total extracellular deficit of sodium in the patient was 187.5 mEq. (30 $\times$ 6.25). This amount of sodium is provided by 1,250 ml. of isotonic saline (each liter of isotonic saline contains 150 mEq. of sodium).

The correction of the electrolyte and water deficits alone, however, does not represent optimal therapy and will prove to be only of temporary benefit. Supplemental hormones must be administered not only for the acute crisis but also for the remainder of the patient's life. The proper choice of the many agents available depends on the needs of the individual patient. In an acute crisis with marked dehydration and peripheral collapse, it is safer to use the whole adrenal cortical extract (ACE) because its salt retaining effect is not marked. If the more potent desoxycorticosterone acetate (DOCA) is employed under such circumstances, a marked increase in the blood volume will result and may cause acute

congestive heart failure. When the whole adrenal cortical extract is given, large amounts must be employed, gauged by the clinical response. An initial dose of 2 ml. per kg. of body weight is injected intravenously and, simultaneously, 5 to 10 ml. is administered intramuscularly. The intramuscular dose is repeated every 3 hours until a clinical response is obtained. Evidence for such a response is an improvement in the hydration, circulation, and blood pressure. Once this result has been obtained, daily intramuscular injections of desoxycorticosterone acetate (DOCA) may be given. The dose of DOCA is empiric, as is demonstrated in our patient. A dose of 1 to 3 mg. is started and increased gradually until the serum sodium level is normal. Subsequently, the DOCA dosage is decreased until the patient's maintenance dose is achieved. In our patient this maintenance dose was 2 mg. per day (Figure 1). If hypoglycemia is a problem, one may elect to utilize one of the parenteral glucocorticosteroids, e.g., hydrocortisone. The intravenous dose of this substance is 3 mg. per kg. of body weight. It is important to recognize that while the glucocorticosteroids also exert a salt retaining effect, it usually is not adequate to correct completely the electrolyte imbalance of adrenal insufficiency. In other words, almost every patient with adrenal failure will require one of the salt regulatory hormones, e.g., desoxycorticosterone acetate (DOCA).

Once the acute crisis has been overcome, the problem of maintenance therapy must be solved. The use of glucocorticosteroids alone has been advocated[1]. This would have the tremendous advantage of oral medication but does not appear to be practical since glucocorticosteroids alone seldom will correct the sodium and chloride deficit. In addition, when the glucocorticosteroids are administered, the hazard of infection must be considered and prophylactic antibiotics must be prescribed. It would seem that the role of the glucocorticosteroids in adrenal failure must be a secondary one, viz., to combat hypoglycemia when it is a problem. Parenteral DOCA must be given to the majority of patients with Addison's disease. One may continue to inject DOCA daily, but once a maintenance level has been determined, pellets may be implanted subcutaneously; these continue to act for 6 to 9 months. Each 75 mg. pellet releases an equivalent of about 0.3 mg. of DOCA each day and the number of pellets to be implanted depends on the previously determined maintenance dose. As an example, our patient needed 2 mg. of DOCA daily; therefore, 6 pellets were used.

The requirement for extra dietary salt should not be neglected. In general, children with Addison's disease need 3 to 5 gm. of sodium chloride each day. However, from a practical point of view, the child will satisfy his own salt needs by supplementing his diet with salt in one form or another.

The outlook for the patient with chronic adrenal insufficiency is not good. Even with adequate treatment, when a stress situation occurs, e.g., infection, operations, etc., there is a tendency for an acute crisis to occur.

SUMMARY

The case history of a 10 year old white male child with chronic adrenal insufficiency probably due to idiopathic atrophy of the adrenal glands has been presented. This patient had a classical picture in that his initial clinical features were those of an acute adrenal crisis. The cardinal features were vomiting, continued voiding in the presence of marked dehydration, and a failure of the dehydration to respond to water and electrolyte replacement therapy alone. The important laboratory findings were low serum sodium chloride and elevated serum potassium levels, a low carbon dioxide combining power, a fasting hypoglycemia with a flat glucose tolerance curve, and failure of the total circulating eosinophils to fall and urinary 17-ketosteroid excretion to increase in response to the intravenous administration of ACTH. The importance of using isotonic or hypertonic sodium chloride in the initial therapy of acute adrenal failure has been emphasized; failure to do so may produce water intoxication. In the management of the acute crisis and also in maintenance therapy, the salt-regulatory hormones appear to be best. The role of the glucocorticosteroids (cortisone, etc.) in the treatment is probably secondary since, in most instances, these substances alone will not be able to maintain electrolyte balance.

REFERENCE

1. Paterson, D., and McCreary, J. F.: Pediatrics, p. 360 J. B. Lippincott Co., Philadelphia and Montreal, 1956.

SYDENHAM'S CHOREA

Bernard J. Walsh, M.D.,* Reginald S. Lourie, M.D.†

INTRODUCTION

Since rheumatic fever is now much less frequent than it was 10 or 15 years ago, chorea as a manifestation of rheumatic fever has also become much less frequent. Most present-day chorea tends to be rather mild, so that many a physician in a busy general or pediatric practice will never

* Senior Attending Staff, Cardiologist, Children's Hospital; Associate Clinical Professor of Medicine, Georgetown University School of Medicine.

† Senior Attending Staff, Director of Psychiatry, Children's Hospital; Associate Clinical Professor of Pediatric Psychiatry, George Washington University School of Medicine.

encounter it. Statistically, however, chorea continues to occur in about 50 per cent of cases of rheumatic fever.

The following case presents a striking example of moderately severe Sydenham's chorea, including the typical symptom of difficulty in handwriting.

CASE REPORT

This was the first Children's Hospital admission of a 15 year old white girl who complained of unusual body movements of one month duration.

Six weeks before admission she noted difficulty in handwriting. Four weeks before admission there were gross jerky movements of all extremities; these movements were more pronounced in the upper extremities and increased in frequency when she was emotionally disturbed. These abnormalities continued, and two weeks prior to admission facial grimacing became apparent. Subsequently, the patient had increased difficulty in dressing herself; slurred, and frequently interrupted speech, and increased lability of emotions developed. There was no history of past rheumatic fever or of scarlet fever. There was no associated sore throat or fever. Treatment in the 10 days before admission had included bed rest, and the use of promazine (Sparine®) and phenobarbital, all without effect.

Her past history was non-contributory. One aunt had had chorea without known heart disease at the age of 11 years.

On admission to the hospital the patient appeared to be a well-nourished and well-developed white adolescent girl who was not acutely ill. She was cooperative and friendly, but was definitely hyperactive and euphoric. She had purposeless movements of her face, tongue, arms, and legs. Her speech was slurred. Oral temperature was 101 degrees, pulse rate 80 per minute, respirations 30 per minute and blood pressure 140/80. Significant abnormalities included moderately severe cervical lymphadenopathy, purposeless movements of the extremities as previously described (noted more prominently in the right arm), mild weakness of the right arm, hyperextension of the fingers when the arms were extended, slurred and frequently blocked speech when counting, hands positioned back to back when elevated above the head, and a "hung-up" right patellar reflex. No cardiac abnormalities were noted. The remainder of the physical examination was normal. A hemogram and urinalysis were unremarkable. Throat culture grew out pneumococcus but no beta hemolytic streptococcus. Anti-streptolysin O (ASO) titer was 250 units, C reactive protein 3 plus, and corrected sedimentation rate 30 mm. per hour. Chest x-ray revealed normal heart shadow and lung fields. An electrocardiogram performed on two occasions was normal. An electroencephalogram was reported as minimally abnormal and without focus.

The patient's fever increased to 103 degrees, and a maculo-papular pruritic rash appeared on her extremities and trunk within a day of admission. Fever persisted for 5 days but promptly diminished following the administration of aspirin in a dose of 0.6 gm. four times daily. Other therapy included bed rest, penicillin, diphenhydramine (Benadryl®) and phenobarbital. At discharge, 10 days after admission, the patient was afebrile; purposeless movements were decreased; cardiac examination continued to be normal.

DISCUSSION

Dr. Walsh:

Over the years we have divided chorea into two broad groups. First, chorea, accompanied by other manifestations of rheumatic fever, and

second, the so-called "pure" chorea, that is, chorea with no other clinical or laboratory manifestations of rheumatic fever. The former group is the more common. In this group, chorea generally appears several weeks or months after the first symptoms of rheumatic fever occur. Chorea as the first manifestation of rheumatic fever is relatively uncommon; chorea is also almost never seen concurrently with migratory polyarthritis.

Chorea was first recognized a long time ago. Sydenham's classic description is more than 200 years old. It was not until about 100 years ago that the English first began to note that chorea seemed to be related to a condition which caused arthritis in children, rheumatic fever. However, chorea was not well defined as a part of rheumatic fever until the latter part of the last century, or the first part of this century. When Sir William Osler wrote the first edition of his book on internal medicine he described chorea as a manifestation of very severe rheumatic fever. Observations over the years have indicated that this is not true. Chorea is a manifestation of relatively mild rheumatic fever, no matter how severe the chorea.

The incidence of heart involvement in those with chorea as part of the rheumatic disease is definitely less than in those who have rheumatic fever without chorea. Patients with pure chorea have an incidence of rheumatic heart injury not in excess of 20 per cent. This may be contrasted with the 50 per cent incidence of heart involvement in those who have rheumatic fever without chorea. Bland a few years ago reported a 20 year follow up of 1000 patients first seen at the House Of The Good Samaritan in Boston. In his report chorea as a major manifestation of rheumatic fever was associated with a mortality of about 12 per cent. With any other major manifestation of rheumatic fever the mortality was from 2 to 4 times greater.

In the past few months, Dr. Stollerman of Irvington House has described some interesting immunological and bacteriological observations in patients with chorea. He found that patients with chorea who had other clinical manifestations of rheumatic fever had the expected incidence, as this child did, of elevated ASO titer, positive C reactive protein and fast sedimentation rate. Those with "pure" chorea, in the vast majority of instances, had a high antistreptolysin titer early in the course of their chorea. In many instances, although the chorea continued, the ASO titer or C reactive protein returned to normal range. In patients with "non-pure" chorea, the chorea may not appear for two or three months after the initial evidence of rheumatic fever when the ASO titer elevation and all the other evidences of active rheumatic fever had disappeared.

There are some interesting clinical features of chorea such as hemichorea in which the patient will have the manifestations limited to the extremities on one side of the body. Another manifestation is called "limp"

chorea, where there is not much choreiform motion, but the patient walks as if there were hemiparesis.

The management of chorea is the management of rheumatic fever plus the special measures added in accordance with the degree of chorea present. As a rule the actual choreiform manifestations of rheumatic fever are self-limited to a period of weeks but may go on for months, waxing and waning. Some years ago, fever therapy was in vogue; fever was produced with injections of killed typhoid bacilli or milk, or by use of hyperthermia machines. The stress created by the therapy was often far worse than the problem being treated. In recent years, for the rather rare moderately severe chorea, we have used rectal instillations of paraldehyde to keep the patients asleep for most of 2 or 3 days; when they awakened they were markedly improved in most instances.

In general, it is not necessary to use anything but mild barbiturates, and to minimize external stimulation. It is important to reassure the parents and the patient, if he is old enough to understand, that he will recover. I cannot say that permanent brain damage from chorea does not occur, but I have never seen it, even after multiple attacks of chorea. I remember a 12 year old girl who died of rheumatic carditis in heart failure during the active phase of chorea. Both grossly and microscopically, her brain showed nothing abnormal. Except for the initial and prophylactic use of antibiotics for treatment and prevention of any hemolytic streptococcal infection that may be present, there has been very little change in treatment of chorea (and rheumatic fever in general) in the past 50 years. The use of steroid hormones up to this moment has not added any material difference to the prognosis of either chorea or rheumatic fever. Rest and salicylates are still the keystones of treatment.

Dr. Lourie:

I have become convinced that chorea is established on the basis of an inflammatory lesion, and that the psychiatric aspects of the illness are secondary to involvement of mid-brain areas that deal with behavior and control of emotions. Often we are asked to see a child with chorea in order to help establish an etiology for the change in behavior. Particularly when the chorea is mild, it is not an easy task to determine why this child has become so irritable and evasive, avoids situations, and has changed in personality. However, if we can remember that changes may be part of any acute encephalitic picture we can understand the same type of personality change in chorea. One puzzling aspect is that quite frequently chorea is set off by some kind of emotional trigger, such as an accident, a severe fright, or a severe disappointment. We might understand this in theoretical terms as the organism's attempt to maintain a

balance between the cortical functions and mid-brain functions, and of the cortical areas attempting to maintain controls in spite of the presence of mid-brain pathology. However, when something like a sudden stress situation comes along to influence the cortical centers and their controls, the underlying mid-brain pathology becomes evident. The psychiatric aspects of chorea otherwise are related to the child's irritability and upsetness with itself, because it cannot control movement, because it cannot accomplish what it starts out to do and because its relationships with people change. This too is a factor that sometimes results in withdrawal, and needs to be taken into account in the everyday handling and planning for the child with chorea. There are many who feel that considerable sedation is indicated, as well as emphasizing the transitory nature of the illness (in terms of weeks usually) to the child directly.

We have seen at least a dozen children with apparent residual brain damage after repeated attacks of chorea, and this too has emphasized to us the organic nature of the choreic process. As with all types of encephalopathy where there is repeated insult to the brain, there may be residual damage that can influence the level of intelligence, the ability to learn, and the ability to control impulses. In other words, the whole behavior pattern can be a problem which is not truly a part of the chorea but part of the after effects.

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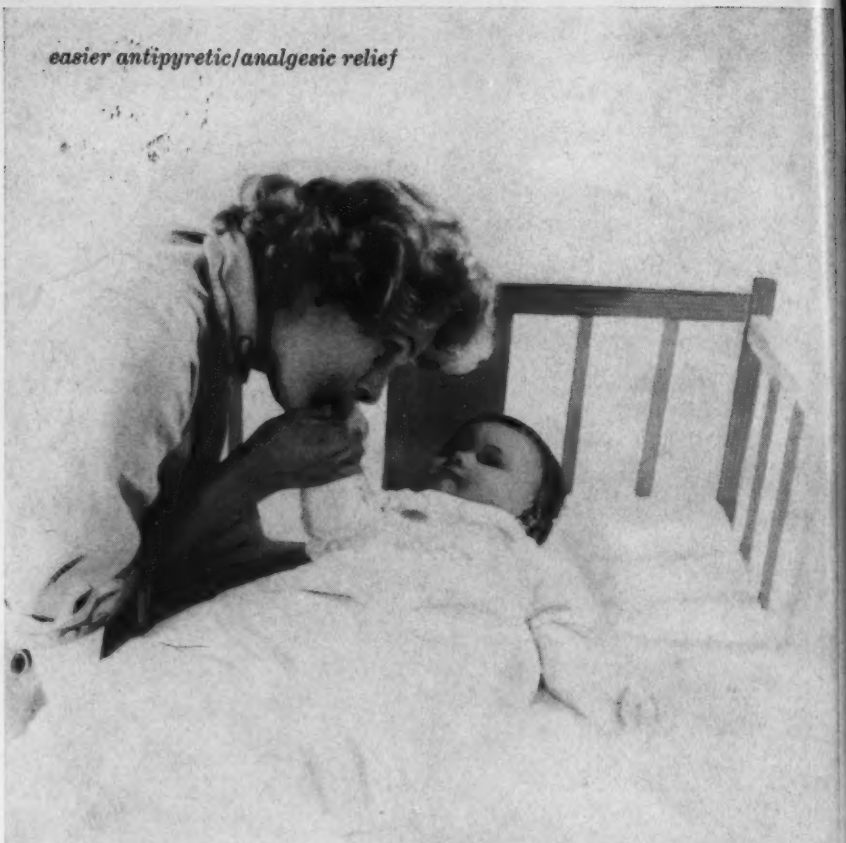

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